REMARKS

Claims 1 to 18 now stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al (Pharm. Research, Vol. 7, No. 4, pgs 379-383, collectively, "Gu") in view of Harris et al (U.S. Patent No. 4,743,450, collectively, "Harris).

The Examiner alleges that Gu et al renders obvious the process of making moexipril magnesium and that Gu discloses a process of making a moexipril alkaline salt by allegedly **reacting** moexipril hydrochloride with an alkaline stabilizing agent . Respectfully no such reaction is taught. The components are merely combined and any reaction is insignificant to the desired end result. Referring now to the publication by Gu et al, "Drug-Excipient Incompatibility Studies of the Dipeptide Angiotensin Converting Enzyme Inhibitor, Moexipril Hydrochloride: Dry Powder vs Wet Granulation", Pharm Res.7(4):370-383, this publication discloses that moexipril hydrochloride can be stabilized by making compositions comprising moexipril hydrochloride and an alkaline stabilizing agent selected from sodium bicarbonate, sodium carbonate and calcium carbonate. It is stated that the stabilization is accomplished only when the compositions are made by a wet granulation process. In the conclusion of the publication, it is postulated that the stabilization in part results from the neutralization of the acidic drug by the basic excipient at the outer surface of the granulated material. It is also stated that it is possible that a portion of the moexipril was converted to alkaline salts via granulation. It thus appears clear that Gu et at teaches that only a portion (if any) of the drug, and only that portion at the outer surface of the granules, may be converted to the alkaline salt, and **that the stable product thus results entirely or primarily not from conversion to alkaline salts, but from stabilization of the moexipril hydrochloride by the presence of the alkaline stabilizing compound in the final product.** Gu et al , discusses , the importance of stabilizing the product in order to avoid cyclization processes and how the stability varied with the ph values. For example, on page 381 at column 2, it was determined that with ph values below 4.5, a significant amount of degradation occurred. However at ph values between 4.5 and 10 the degradation rate was about 10 times slower. Gu also **postulates** only that the stabilization effect may be a result from the neutralization of the acid drug by basic excipients only at the outer surface of the granulated material. However, primarily the product is moexipril hydrochloride as the active. Gu et al is thus consistent with

the teaching of U.S. Pat. No. 4,743,450, which, as set out below, teaches stable compositions comprising the unstable drug, stabilized by the presence of an alkaline compound in the final composition.

The claims are therefore not rendered obvious to one skilled in the art in view of Gu for the reasons that Gu does not motivate one skilled in the art to manufacture moexipril magnesium from Gu's teaching of manufacturing moexipril hydrochloride stabilized with an alkaline stabilizing agent. Nothing else might be inferred from the teachings of Gu et al and even if one were to read Gu et al in view of Harris, the resulting combination would not be more than, respectfully, merely the teachings of Gu or Harris. The critical point is applicant has provided a process and product wherein not just "some" of the outer surface of particles of moexipril hydrochloride might be converted to moexipril's magnesium salt in a random, unpredictable, uncontrolled manner, but that a substantial portion (at least 70%) is converted to moexipril's magnesium salt, by utilizing a sufficient amount of solvent so as to ensure such a reaction to take place.

Applicant previously submitted the Product Monograph for Univasc® (Moexipril Hydrochloride Tablets) hereby incorporated by reference wherein the tablets marketed by Schwarz Pharma (as listed in the FDA Orange Book as per the teachings of United States Patent No. 4,743,450) also hereby incorporated by reference include magnesium oxide; unreacted but combined and functioning as a stabilizer (see first page). The Examiner is again referred to those pages. Full reconsideration is respectfully requested.

United States Patent No. 4,743,450 discloses a process for making the composition comprising quinapril hydrochloride stabilized by combining with an alkaline stabilizing agent. Clearly, there can be no reacting with this process but merely combining of ingredients. Example A refers to a wet granulation method for the manufacture of tablets from the listed materials including quinapril hydrochloride and magnesium carbonate in the amounts indicated which are not reacted but combined. The Examiner is referred to column 1, line 51 wherein it states, that an amount of a stabilizer compound suitable to retard cyclization, hydrolysis, and/or discoloration is contained in the pharmaceutical composition and that the composition is formed by the steps of **"contacting"** the drug with an amount of stabilizer suitable to retard cyclization and/or hydrolysis. It is also stated at the bottom of that

column that the composition will also contain substances which do not interfere with the function of the stabilizing additives.

Referring to column 3, at line 25 of United States Patent No. 4,743,450, the use of the stabilizers is discussed extensively and the manner in which the cyclization and hydrolytic instability of the composition can be stabilized using a suitable quantity, i.e. an effective amount of an alkaline stabilizer which is most preferably magnesium. The amount utilized is any amount which will effectively retard or prevent degradation of the ACE inhibitor components. Further at the same column, discussing the saccharides which might be used, they are selected from substances which do not contain groups which could significantly interfere with the function of either the metal containing component or the drug component. **Further in relation to the excipients they are selected from those that do not interfere with the alkaline earth metal stabilizer's function in the composition.**

The essence therefore of that which is taught and claimed in United States Patent No. 4,743,450 is an ACE inhibitor which is susceptible to cyclization, hydrolysis, and discoloration, in combination with a suitable amount of an alkaline earth in the composition as a stabilizer. No where within the reference is there discussed any reactions, incorrectly concluded by the Examiner. The reference is mute in this regard with the exception of contacting or combining the materials. For the composition to contain a stabilizer, clearly it must not have reacted with the drug, suitable saccharides or suitable excipients. United States Patent No. 4,743,450 merely teaches in Example A, at column 4, that the wet granulation method is used for the manufacture of 5 mg tablets. The reference is silent in relation to anything but the use of a more or less standard wet granulation process. There is no discussion as to how much wetting material should be used, other than Example C, wherein an amount of purified water is indicated but no use for that water is further discussed. Clearly therefore, it is impossible to conclude that United States Patent No. 4,743,450 discloses a process comprising the step of "reacting" since the magnesium compound must remain present in the final composition in order to fulfill its role as a stabilizer.

Clearly therefore one skilled in the art would not expect from a fair reading of Harris that any significant reactions would take place between the ACE inhibitor and the alkaline compound since this would be contrary to the teachings of Harris as set out above. United

States Patent No. 4,743,450 is silent with respect to any reaction as it is sought to stabilize the ACE inhibitor and that the stabilizing compound used must remain functional (not react) and not to be interfered with by any of the saccharides or excipients added to the composition. If it was expected from United States Patent No. 4,743,450 that the stabilizer would react then why would the above mentioned caution be set out clearly in the specification. Clearly, therefore the United States Patent No. 4,743,450 reference teaches combining or contacting but in no way discusses a reaction taking place, although the Examiner has respectfully mistakenly reached that conclusion.

In Applicant's process sufficient water is introduced (as a solvent) in the process to moisten and to thereby permit a reaction to occur. There is no discussion or teaching in United States Patent No. 4,743,450 relating to this process. The Examiner may have incorrectly concluded that a reaction of quinapril and magnesium carbonate is inherent to the combination of the materials, **and incorrectly** that Harris discloses a process of making a solid pharmaceutical composition comprising quinapril magnesium when United States Patent No. 4,743,450 is entirely silent in this regard.

Respectfully therefore, claims 1-18 of the present application cannot be refused as being obvious to one skilled in the art over Gu et al in view of United States Patent No. 4,743,450, since there is no motivation to react the ACE-inhibitor with the alkaline agent but merely to combine it so that the alkaline agents can act as stabilizers as set out above. Clearly nowhere within such a purported combination is there taught:

> *"A process of making a solid pharmaceutical composition comprising moexipril magnesium, said process comprising the step of reacting moexipril or an acid addition salt thereof with an alkaline magnesium compound in the presence of a sufficient amount of solvent so as to convert at least 70% of the moexipril or moexipril acid addition salt to moexipril magnesium."*

Clearly, a process of making a solid pharmaceutical composition comprising moexipril magnesium is taught by Applicant. Neither Gu et al or United States Patent No. 4,743,450 nor any combination of the teachings thereof teach such a process or the resulting composition . Moexipril magnesium is only a result of Applicant's process which includes

the step of **reacting** (emphasis added) moexipril or an acid addition salt thereof with an alkaline magnesium compound to convert at least 70% of the moexipril or acid addition salt thereof to moexipril magnesium. Applicant is not risking any unknown side reactions but is taking specific steps to provide specific desired results. To do so a solvent must be present in order for the reaction to occur, and the solvent must be present in an amount so as to convert at least 70% of the moexipril or moexipril acid addition salt to moexipril magnesium. This simply is not taught directly or indirectly in Gu et al or United States Patent No. 4,743,450 and further in any combinations thereof. There is no discussion whatsoever of the conversion at least 70% of the moexipril or moexipril acid addition salt to moexipril magnesium as a solid pharmaceutical composition in any of the references cited herein by the U.S. Examiner. A reaction is not disclosed, inferred, suggested or discussed in Harris whatsoever. In fact only the stabilizing activity of the magnesium compound is discussed and the importance of avoiding excipients and saccharides which might interfere with that stabilizing function. Gu et al postulates that a minor insignificant portion may react but the stabilization is a result of the combination of the moexipril hydrochloride with the alkaline stabilizer as evidenced by the Product Monograph previously provided. No other conclusion can be reached.

Clearly all claims depend from Claim 1 except 14. How therefore could they lack an inventive step if Claim 1 is in fact inventive over Gu et al in view of Harris which Applicant has correctly concluded and argued, in spite of the assertions of the Examiner. Claims 2-13 and 15-18 refers to the compound further comprise additional limiting steps of adding the moexipril or acid addition salt thereof and the alkaline magnesium compound to the solvent and mixing in the liquid state and subsequently evaporating the solvent to obtain a dried material and further processing the dry material into a solid pharmaceutical composition. For the same reasons therefore set out in relation to Claim 1, Claims 2-13 and 15-18 would therefore be novel and non-obvious as would claim 14.

No reference is made to moexipril magnesium in United States Patent No. 4,743,450. None of the teachings discuss or even infer the compound moexipril magnesium in that the final compound quinapril magnesium does not necessarily require a stabilizer as set out in the teachings of Applicant's invention. However, United States Patent No. 4,743,450 includes a stabilizer; Applicant's compound does not.

All the dependent claims are therefore inventive in view of the argument set out above since none of Gu et al alone or in any combination with United States Patent No. 4,743,450 teaches the invention, moexipril magnesium.

Referring to the traditional test enunciated in Graham vs. John Deere Company 383 U.S. 1, 148 U.S.P.Q. 459 1966, Applicant has followed the Section 103 nonobviousness requirement set out therein The scope and content of Gu et al and Harris has been determined, and the differences between the prior art and the claims at issue have been ascertained. The patentability of the claims at hand stem from the fact that the specific combination of the claimed elements was not disclosed in Gu et al or Harris or any combinations thereof and the specific combination of claimed elements was nonobvious to one of ordinary skill in the art. Clearly there is no motivation within Gu et al or Harris or Gu et al in view of Harris to arrive at Applicant's amended claim set. The moexipril hydrochloride and magnesium carbonate are capable of an acid-base reaction. It is difficult to control the process so as to completely avoid an acid-base reaction in the making of the composition. The exact composition of the final product is thus uncertain and probably variable, if the teaching of Gu et al in view of U.S. Pat. No. 4,743,450 is followed. No motivation however from either reference to do so is present from a fair reading of either reference. Full reconsideration is respectfully requested.

Clearly, the prior art does not suggest or provide any reason or motivation to make such a modification as purported by the Examiner. With reference to In Re: Regal, 526 F. 2d 1399, 1403 n. 6, 188 USPQ 136, 139 n. 6 (CCPA 1975).

> "There must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references".

In Re: Geiger, 815 F. 2d 686, 688, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987) (obviousness can not be established by combining pieces of prior art absence some "teachings, suggestion, or incentive supporting the combination"): In Re: Cho. 813 F. 2d 378, 382, 1 USPQ 2d 1662, 1664 (Fed. Cir. 1987)("discussing the Board's holding that the artisan would have been motivated to combine the references").

Therefore, it Applicant's view there is no evidence of motivation in the prior art, either within the references themselves, or knowledge generally available to one of ordinary skill in

the art, to make the purported changes suggested by the Examiner to arrive at the claimed subject matter.

Respectfully, the Examiner is creating a 20/20 hindsight reconstruction using Applicant's invention as a blue print to allegedly find elements of Applicant's combination in the prior art. This is not permissible as set out below.

Even if one skilled in the art were to combine Gu et al with Harris they would arrive at moexipril hydrochloride which is stabilized by an alkaline agent and preferably magnesium oxide as per the product monograph of the moexipril hydrochloride tablets manufactured by Schwarz Pharma attached in the prior Information Disclosure Statement provided. Applicant is not "combining" but is "reacting" the active and the agents to result in the moexipril magnesium.

In fact it is well established that for a combination of references to render an invention obvious, it must be obvious that the references can be combined; In Re Avery 186 U.S.P.Q.161 (CCPA 1975). The references themselves and not in retrospect, must suggest what has to be done. In Re: Skoll 187 USPQ 481 (CCPA 1975). There must be some reason for the combination other than hindsight gleaned from their invention itself. Interconnect Planning Corp., vs. Feil, 774 F. 2d 1132, 1134 (Fed. Cir. 1985). See also Panduit Corp. vs. Dennision Mfg. & Co., 810 F. 2d 1561, 1568 (Fed. Cir. 1988) where the court said:

> "Elements of separate prior art patents cannot be combined when there is no suggestion of such combination anywhere in those patents".

Although the Examiner suggests that the structure could readily be modified to form a combination of the claims at issue, the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. Please See in Re: Gordon 733 F. 2d 900-902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); In Re: Grabiak, 769 F. 2d 729, 731, 226 USPQ 870, 872 (Fed. Cir. 1985).

Again respectfully, the Examiner is creating a 20/20 hindsight reconstruction using Applicant's invention as a blue print to allegedly find elements of Applicant's combination in the prior art. This is not permissible as set out below.

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

> *"Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the Examiner relied upon hindsight to arrive at the determination of obviousness. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."*

Clearly there is no motivation within Gu et al to modify his composition into Applicant's process absent some teaching in Gu et al to do so with or without the teachings of Harris, which is simply not the case.

ATD Corporation v. Lydall, Inc., 48 USPQ 2d 1321, 1329 (Fed. Cir. 1998)

> Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. **There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.(emphasis added)**

In re Oetiker, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992)

> The combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a prima facie case of obviousness. **There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination.** (emphasis added)That knowledge can not come from the applicant's invention itself.

Hindsight is not appropriate when considering the claim set of Applicant.

In Re: Rouffet, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998)

> *"As this court has stated, "virtually all [inventions] are combinations of old elements." Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were*

sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 USPQ 2d 1551, 1554 (Fed. Cir. 1996).

To prevent the use of hindsight based on the invention to defeat patentability of the invention, ***this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*** (emphasis added)

This court has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. In this case, the Board relied upon none of these. Rather, just as it relied on this high level of skill in the art to overcome the differences between the claimed invention and the selected elements in the references, it relied upon the high level of skill in the art to provide the necessary motivation. The Board did not, however, explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the field of art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Because the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, ***this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness.*** (emphasis added)*See In re Gorman, 933 F.2d 982, 986, 18 USPQ 2d 1885, 1888 (Fed. Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen and Ruddy."*

Applicant further submits that a correct and recent statement of the law of obviousness is presented within Windsurfing International Inc. and Fred Ostermann GMBH et al, in the Re: Sernaker reasoning of the Court of Appeal 702 F.2d 989 (Federal Circuit 1983) when it was concluded that the following related test are appropriate standards against which to make an obviousness determination:

(a) whether a combination of the teachings of all or any of the references would have suggested (expressly or by implication) the possibility of

achieving further improvement by combining such teachings along the line of the invention in suit, and

(b) whether the claimed invention achieved more than a combination which any or all of the prior art references suggested expressly or by reasonable implication.

Referring to the Windsurfing case, it was determined that although the test (a) was satisfied, the test (b) was not satisfied because the prior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings. It was therefore concluded that the patented invention in the Windsurfing case resulted in more than a combination suggested by any of the prior art references. Applicant submits this has been determined with the amendments and arguments presented above.

In view of the above submissions, Applicant respectfully submits that the amended claims in the Application are clearly allowable over the prior art, and full reconsideration is requested.

Further in relation to obviousness the following cases are emphasized for the Examiner's information:

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

"Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the Examiner relied upon hindsight to arrive at the determination of obviousness. ***It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious****(emphasis added). The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."*

In Re: Rouffet, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998)

"As this court has stated, "virtually all [inventions] are combinations of old elements." Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate

patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 USPQ 2d 1551, 1554 (Fed. Cir. 1996).

To prevent the use of hindsight based on the invention to defeat patentability of the invention, ***this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*** (emphasis added)

This court has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. In this case, the Board relied upon none of these. Rather, just as it relied on this high level of skill in the art to overcome the differences between the claimed invention and the selected elements in the references, it relied upon the high level of skill in the art to provide the necessary motivation. The Board did not, however, explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the field of art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Because the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, ***this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness.*** (emphasis added)*See In re Gorman, 933 F.2d 982, 986, 18 USPQ 2d 1885, 1888 (Fed. Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen and Ruddy."*

Should the Examiner have any questions he/she is respectfully requested to contact Neil H. Hughes at (905) 771-6414 at his/her convenience.

Respectfully submitted,

Neil H. Hughes, P.Eng.
Registration No. 33,636
Agent for the Applicant

NHH:mse
Enclosures